Paclitaxel Plus Vinorelbine in Metastatic Breast Ca Patients With Contraindications to Receive Anthracyclines

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Thirty-three metastatic breast cancer patients with prior chemotherapy (adjuvant alone, 9 patients; chemotherapy for metastatic disease alone, 13 patients; chemotherapy for both, 11 patients) received paclitaxel (Taxol) 135

Metastatic breast cancer belongs to the group of moderately sensitive malignant tumors. Classic combination chemotherapy regimens, especially those containing anthracyclines (FAC, FEC, AC, and others) result in objective responses in 50% to 80% of patients, including complete responses in nearly 15%.[1] However, in spite of the important research conducted over the past two decades, metastatic breast cancer remains essentially an incurable disease, with the vast majority of patients presenting with a recurrence of disease after initial chemotherapy. In particular, the prognosis of metastatic breast cancer patients who are not candidates for the new anthracycline therapy (because of prior anthracycline resistance, prior anthracycline cumulative dose reaching the maximum recommended dose, or medical contraindications to receive anthracyclines) has been considered extremely poor.

Over the past decade, a few new drugs, such as the taxanes (paclitaxel [Taxol] and docetaxel [Taxotere]) and vinorelbine (Navelbine), have been shown to be partially non-cross resistant with anthracyclines in metastatic breast cancer. The availability of these drugs may give patients with contraindications to receive anthracyclines the opportunity to receive new chemotherapy regimens able to induce a substantial rate of objective responses. The encouraging antitumor activity of paclitaxel (21% to 22% response rate) and vinorelbine (16% response rate), as single agents in metastatic breast cancer patients refractory to anthracyclines,[2-4] prompted us to evaluate the antitumor activity of the combination of these two drugs in patients with contraindications to receiving anthracycline therapy. This article presents the preliminary results of our cooperative phase II study using this combination.

Criteria for Patient Selection

Eligibility criteria included histologically proven breast cancer, progressive metastatic tumor, measurable or clearly evaluable disease in at least one site, prior treatment with at least a chemotherapy regimen, Karnofsky performance status of 70% or more, life expectancy of at least 2 months, adequate bone marrow, liver, and renal functions, and a contraindication to receive anthracyclines (anthracycline-refractory disease, cumulative dose of anthracyclines reaching the maximum recommended dose, or myocardiopathy). Prior hormonal therapy was allowed if it ended at least 1 month before chemotherapy. A signed, informed consent indicating that patients were aware of the investigational nature of the study, as prescribed by the institutional policy of each center, was required for all patients.

Baseline assessment included a full history and complete physical examination with a specific record of all measurable and evaluable sites of neoplastic disease, complete blood cell (CBC) counts with differential, electrolytes and liver function chemistries, and a chest x-ray. Additional radiographic and echographic studies, as well as photographs of all apparent cutaneous or nodal lesions, were obtained as clinically indicated to document measurable or evaluable disease. At the beginning of each new course of therapy, a complete blood count with differential and electrolytes and liver function chemistries were obtained from all patients. Echotomographies or computed tomographies, chest x-rays, and photographs were repeated every three courses in the case of liver, lung, and cutaneous/nodal lesions, respectively, to document response to the combination.

Chemotherapy treatment consisted of paclitaxel 135 mg/m² over 1 hour followed by vinorelbine 30 mg/m² over 10 minutes on day 1 every 3 weeks. Patients received premedication with dexamethasone (20 mg IV), cimetidine (200 mg IV) and dexchlorpheniramine (5 mg IV) or another
antihistaminic drug just before paclitaxel administration. In case of neutropenic fever, dosage of both drugs was reduced by 25% for the remaining courses of therapy.

Patients received at least three courses of paclitaxel plus vinorelbine before response was evaluated, except for those who had overt progression of disease or died after the first or second course of treatment. These patients were categorized as having progressive disease and were considered assessable for response, according to an intention-to-treat analysis. Patients with stable disease, a partial response, or a complete response received the combination until they developed progressive disease, severe extramedular toxicity or completed a maximum of eight courses. Response and toxicity were categorized according to WHO criteria.[5]

**Results of the Study**

By June 1997, 38 patients had entered the study, which is currently ongoing. Thirty-three of these patients either received three or more courses of therapy, or progressed or died after the first or second courses, and are considered evaluable for response and toxicity. The characteristics of these 33 patients are shown in Table 1. Most patients were postmenopausal, presented involvement of three or more organ systems, and had visceral disease.

The median number of courses given per patient so far is five, although some patients are still under treatment. Three patients received only one course of treatment because of clear progression of the disease or tumor-related death at the end of the first treatment. Several patients were able to receive eight courses of therapy without significant toxicity.

Three complete and 13 partial responses have been observed to date among the 33 evaluable patients (overall response rate of 48.5%, 95% confidence interval, 31% to 66.5%). Table 2 shows the distribution of responses by metastatic site. Responses have been seen in soft tissues, lymph nodes, lung, and liver. The response rate was similar in patients with bilaterally measurable disease (10/20, 50%) and evaluable disease (6/13, 46%).

The response rate in patients receiving paclitaxel plus vinorelbine as first-line chemotherapy for metastatic disease was 67% (6/9) compared to 42% (10/24) for those receiving the treatment as second- or third-line chemotherapy for metastasis. The response rate among the 10 patients with primary anthracycline resistance (no response or progression during prior anthracycline treatment) was 60%.

Grade 3 alopecia has been the most common side effect of treatment (Table 3). Sixteen percent of patients had neutropenic fever. Peripheral neuropathy was frequent but only mild to moderate. Phlebitis was a significant problem in those receiving the combination through a peripheral vein. One patient had vinorelbine extravasation resulting in skin ulceration. No toxic deaths occurred. Seven patients (21% of total population) had 25% dose reductions due to febrile neutropenia (five patients) or asthenia (two patients). The two patients who needed dose reductions due to asthenia were quite elderly (77 and 78 years), had doxorubicin-resistant disease, and achieved partial responses with the combination. Both were able to continue treatment after dose reduction.

**Discussion**

Our study shows that the combination of paclitaxel and vinorelbine given on day 1 every 3 weeks is active and well tolerated in metastatic breast cancer patients with contraindications to receive anthracyclines. This combination regimen was designed according to previous reports showing the activity of both paclitaxel and vinorelbine in metastatic breast cancer patients refractory to anthracyclines and the partial lack of cross-resistance between paclitaxel and vinorelbine in the same population.[6] A response rate of nearly 50% in this population is remarkable, because all patients had previous exposure to chemotherapy (the vast majority including anthracyclines) and two thirds of the patients presented with visceral involvement. These data suggest that there is a clinical synergism between paclitaxel and vinorelbine in metastatic breast cancer.

As a matter of the fact, the response rate observed with this combination in our study seems superior to the mere addition of the expected response rates of these drugs when used as single agents in the same patient population.[2-4] Our results are in agreement with those of Michelotti et al, who administered paclitaxel (day 1) plus navelbine (days 1 and 8 or 1 and 3) to 37 breast cancer patients with extensive prior chemotherapy, observing a response rate of 38%. [7]

On the other hand, the combination was well tolerated by the patients. Our main concern before starting the study was the possible synergistic neurotoxic effect of paclitaxel and vinorelbine. Because of this, we designed this regimen with relatively low doses of paclitaxel in combination with vinorelbine administered in just 1 day every 3 weeks. With this schedule, neurotoxicity was really not
a clinical problem. In addition, myelosuppression was mild, so that more than 75% of patients did actually receive the planned chemotherapy dose. Finally, this schedule is easy to administer (less than 2 hours of outpatient administration) and convenient, requiring patients to visit the hospital only once every 3 weeks. This, together with the relatively low doses of paclitaxel, results in a reduction of the cost of treatment in relation to the cost of other paclitaxel-containing regimens advocated for salvage treatment of anthracycline-resistant breast cancer patients.

In conclusion, the preliminary results of our study with paclitaxel and vinorelbine suggest that this schedule is active and well tolerated in metastatic breast cancer patients with contraindications to receive anthracyclines. Further follow-up and additional patients are needed in order to define more precisely the activity and tolerance of the treatment.

References:


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